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Clinical Benefit of Glycoprotein IIb/IIIa Blockade With Abciximab Is Independent of Gender

Pooled Analysis from EPIC, EPILOG and EPISTENT Trials

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OBJECTIVES We sought to determine the efficacy and safety of platelet glycoprotein IIb/IIIa receptor (GP IIb/IIIa) blockade with abciximab in women undergoing percutaneous coronary intervention.

BACKGROUND Although gender differences in response to platelet glycoprotein IIb/IIIa receptor blockade have been described, there have been no large clinical studies to assess these differences.

METHODS Outcomes were determined using meta-analysis technique.

RESULTS In the pooled analysis, the primary end point of death, myocardial infarction (MI) or urgent revascularization within 30 days was reduced from 11.3% to 5.8% ($p < 0.001$) in men and from 12.7% to 6.5% ($p < 0.001$) in women treated with abciximab. At six months, death, MI or urgent revascularization was reduced from 14.1% to 8.3% ($p < 0.001$) in men and 16.0% to 9.9% ($p < 0.001$) in women receiving abciximab. At one year, mortality was reduced from 2.7% to 1.9% ($p = 0.06$) in men and 4.0% to 2.5% ($p = 0.03$) in women treated with abciximab. Major bleeding events occurred in 2.9% versus 3.0% ($p = 0.96$) of women and 2.7% versus 1.3% ($p = 0.003$) of men treated with placebo versus abciximab, respectively. Minor bleeding events occurred in 4.7% versus 6.7% ($p = 0.01$) of women and 2.3% versus 2.2% ($p = 0.94$) of men treated with placebo versus abciximab, respectively.

CONCLUSIONS This pooled analysis demonstrated no gender difference in protection from major adverse outcomes with GP IIb/IIIa inhibition with abciximab. Although women had higher rates of both major and minor bleeding events with abciximab compared with men, major bleeding in women was similar with and without abciximab. There was a small increased risk of minor bleeding with abciximab in women. (J Am Coll Cardiol 2000;36:381–6) © 2000 by the American College of Cardiology

Atherosclerotic heart disease is the leading cause of morbidity and mortality in women in the U.S. (1–2). Percutaneous coronary revascularization remains the most frequently performed procedure in women over 65 years of age (3). However, women may have a higher incidence of poor outcome after percutaneous coronary intervention (PCI) compared with men (4–5). Mechanisms responsible for these findings may include older age, higher incidence of comorbidities and smaller coronary arteries and body size in women (6). However, there has been an interesting body of literature reporting increased platelet function in women as another mechanism explaining the "gender gap" (7–16), suggesting that women would benefit more than men from glycoprotein IIb/IIIa (GP IIb/IIIa) blockade.

Although the role of GP IIb/IIIa blockade during coronary intervention has been established, there has been some conflicting data regarding the use of these agents in women. This current study examines the aggregate data from the three large randomized trials of abciximab (ReoPro, Centocor, Malvern, Pennsylvania), Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC, 14), Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG, 15) and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT, 16) in the setting of PCI to evaluate the influence of gender on outcome and treatment effect with GP IIb/IIIa blockade.

METHODS

Study group. Prospective data were collected from patients undergoing PCI enrolled in the EPIC, EPILOG and EPISTENT trials (17–19). The details of the inclusion and exclusion criteria and trial designs have been published elsewhere. Briefly, the inclusion criteria for EPIC included: 1) acute myocardial infarction (MI) with primary or rescue angioplasty within 12 h of symptom onset; 2) early postinfarction angina or unstable angina with electrocardiographic evidence of ischemia; or 3) high-risk lesion morphology with advanced age, female gender or diabetes mellitus. There were 392 women and 1,012 men enrolled in the trial who were treated with either placebo or the bolus and infusion regimen of abciximab. Inclusion criteria for EPILOG included elective or urgent percutaneous coronary revascularization, excluding patients with acute MI or un-

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Abbreviations and Acronyms

ACC/AHA	=	American College of Cardiology/American Heart Association
ACT	=	activated clotting time
CABG	=	coronary artery bypass graft
CHF	=	congestive heart failure
EPIC	=	Evaluation of 7E3 for the Prevention of Ischemic Complications trial
EPILOG	=	Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade trial
EPISTENT	=	Evaluation of Platelet IIb/IIIa Inhibitor for Stenting trial
GP IIb/IIIa	=	Glycoprotein IIb/IIIa receptor
MI	=	myocardial infarction
PCI	=	percutaneous coronary intervention
PTT	=	partial thromboplastin time

stable angina according to the EPIC criteria. There were 780 women and 2,012 men enrolled in the trial. Inclusion criteria for EPISTENT were patients referred for elective or urgent PCI who were suitable candidates for either conventional angioplasty or coronary stent implantation. There were 599 women and 1,800 men enrolled in the trial. Overall, there were 6,595 patients, of whom 1,771 (26.9%) were women and 4,824 (73.1%) were men.

Protocols. In the three trials, all patients were treated with aspirin. In EPIC, patients were randomized to placebo, abciximab bolus only (0.25 mg/kg) or abciximab bolus followed by a 12 h infusion (10 μg/min). Heparin was given in all three arms with initial bolus dose of 10,000 to 12,000 U. In the EPILOG trial, patients were randomized to placebo with standard-dose, weight-adjusted heparin (100 U/kg, target activated clotting time [ACT] $\leq$ 300), abciximab bolus followed by 12 h infusion (0.125 μg/kg/min, maximum 10 μg/min) with standard-dose, weight-adjusted heparin or abciximab bolus and infusion with low-dose, weight-adjusted heparin (70 U/kg, ACT $\geq$ 200). In EPISTENT, patients were randomized to stent and placebo with standard-dose, weight-adjusted heparin, stent and abciximab bolus and infusion with low-dose, weight-adjusted heparin or balloon angioplasty and abciximab bolus and infusion with low-dose, weight-adjusted heparin.

Study end points. The primary end point for these trials was a composite of death from all cause, MI or reinfarction or severe myocardial ischemia requiring urgent revascularization by either PCI or coronary artery bypass grafting (CABG) within 30 days after randomization. A second end point was a composite of death, MI or urgent revascularization within six months after randomization. For the long-term follow-up at one year, mortality was used. End point classifications of clinical events committees, blinded to treatment assignment, were used for the final analysis. An end point of in-hospital, MI was defined by one of two criteria: new, clinically significant Q waves in two or more contiguous electrocardiographic leads or elevation in creatine kinase or its MB isoenzyme to at least three times the upper limit of normal. After discharge from the hospital, MI was defined by the occurrence of new Q waves in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to more than twice the upper limit of normal. The MB isoenzyme value was used if it was available; if not, the total creatine kinase value was used.

Bleeding events were classified as major or minor according to the criteria used by the Thrombolysis in Myocardial Infarction Study Group (17). Hemorrhage was defined as major if there was a reduction of hemoglobin of more than 5 g/dl (or $\geq$15% in hematocrit) or any intracranial bleeding (17). Minor bleeding was defined as observed blood loss with reduction in hemoglobin of more than 3 g/dl but less than or equal to 5 g/dl (or 10–15% reduction in hematocrit) if there was spontaneous gross hematuria or hematemesis, even if the hemoglobin or hematocrit drop was less or equal to 3 g/dl or less than 10% respectively or, if there was no observed blood loss, a reduction of more than 4 g/dl in hemoglobin or 12% or more in hematocrit (17). Hemoglobin and hemotocrit were measured before and 12 to 36 h after initiation of the study agent and at the time of discharge (14–16). All suspected occurrences of stroke or intracranial hemorrhage were adjudicated by an independent neurologist.

Statistical analysis. Pooled abciximab bolus and infusion versus placebo groups were analyzed by gender. Individual patient data for all three trials were combined. We excluded the abciximab bolus only group because this dosing was found to be ineffective in reducing ischemic complications and was used only in the EPIC trial. Efficacy was analyzed on an intention-to-treat basis with use of Pearson's chi-square test and Mantel-Haenszel statistics. A combination of 13 baseline and angiographic characteristics, in addition to gender, was used for multivariate logistic regression modeling for the combined cohort of data. These included age, prior PCI, prior CABG, hypertension, diabetes, smoking status, history of congestive heart failure (CHF), prior MI, American College of Cardiology/American Heart Association (ACC/AHA) type B2 or C lesions, thrombus, bypass graft lesions and treatment with abciximab.

The separate analysis of bleeding by gender compared pooled individual patient data from EPILOG and EPISTENT who received low-dose, weight-adjusted heparin and abciximab to those patients who received standard-dose heparin without abciximab. We excluded the standard-dose, heparin arms with abciximab in EPIC and EPILOG, as the EPILOG trial showed that low-dose, weight-adjusted heparin was as effective as standard-dose, weight-adjusted heparin during abciximab therapy but with fewer bleeding complications. A combination of 20 demographic and angiographic characteristics, in addition to gender, was used for multivariate logistic regression modeling. These

Table 1. Demographics

	Men (n = 4,824)	Women (n = 1,771)	p Value
Age (yrs)*	58.5 ± 10.7	62.9 ± 10.4	< 0.001
Caucasians (%)	91.1	88.3	< 0.001
Prior PCI (%)	22.0	18.7	0.004
Prior CABG (%)	12.7	9.6	< 0.001
Hypertension (%)	52.3	65.3	< 0.001
CHF (%)	5.3	9.4	< 0.001
Diabetes (%)	19.4	30.3	< 0.001
Prior MI (%)	53.8	42.6	< 0.001
Worst lesion (%)			
Type B2	57.4	55.7	0.03
Type C	17.0	15.1	
Length (%)			
10–20 mm	38.7	36.5	0.18
>20 mm	9.6	9.1	
Eccentricity (%)	66.8	65.8	0.47
Lesion angulation (%)			
45–90	14.9	17.1	
>90	1.4	2.1	0.02
Irregular contour (%)	53.6	48.7	< 0.001
Ostial (%)	8.1	7.7	0.61
Calcification (%)	10.7	12.0	0.14
Thrombus (%)	17.9	14.8	0.003
Bifurcation (%)	7.4	7.1	0.40
Bypass grafts (%)	2.6	1.3	< 0.001

*Age ± standard deviation.

CABG = coronary artery bypass graft; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

included age, body weight, diabetes, use of abciximab, hypertension, use of ticlopidine or aspirin or other anticoagulant, race, smoking status, residency of the patient and activated clotting time. The adjusted odds ratios, confidence intervals and p values for all significant variables are reported.

RESULTS

The demographics of the pooled gender groups are shown in Table 1. Women were, on the average, five years older and had more comorbidities than their male counterparts, including hypertension, CHF and diabetes. However, men were more likely to have had prior PCIs, CABG and a history of MI and smoking. Overall, women had slightly fewer type B2 lesions but more lesions with acute angulations. However, men had more thrombus-containing and vein graft lesions.

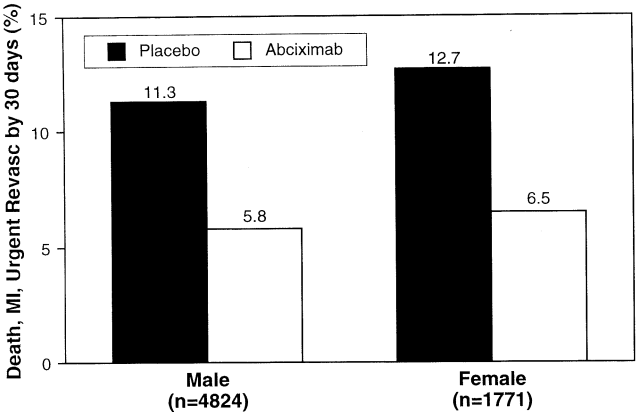

Figure 1. Primary composite end point of death, MI or urgent revascularization at 30 days. $p < 0.001$ for both male and female patients. MI = myocardial infarction; Revasc = revascularization.

Pooled analysis. The primary end point—a composite death, MI or need for urgent revascularization in the first 30 days—was reduced from 11.3% to 5.8% (49% relative risk reduction, $p < 0.001$) in men and from 12.7% to 6.5% (49% relative risk reduction, $p < 0.001$) in women treated with abciximab (Fig. 1). For men and women treated with abciximab, there was no statistical difference in the 30-day end point, 5.8% versus 6.5% ($p = 0.40$), respectively. There was no gender difference in the magnitude of treatment effect achieved with abciximab in the pooled analysis or in the individual trials at 30 days (Table 2). The treatment effect of abciximab was maintained to six months and to one year in both men and women. At six months, death, MI or urgent revascularization was reduced from 14.1% to 8.3% (relative risk reduction of 41%, $p < 0.001$) in men and 16.0% to 9.9% (relative risk reduction 38%, $p = 0.01$) in women receiving abciximab. There was no difference in treatment benefit with abciximab between men and women at six months. At one year, mortality was reduced from 2.7% to 1.9% (30% relative risk reduction, $p = 0.06$) in men and 4% to 2.5% (38% relative risk reduction, $p = 0.03$) in women treated with abciximab at one year. Clinical benefit with GP IIb/IIIa blockade with abciximab was independent of gender. By multivariate logistic regression, abciximab use was independently associated with improved outcome at 30 days, six months and one year (Fig. 2). The factors associated with poor outcome were hypertension, history of MI,

Table 2. Thirty-Day and Six-Month Primary End Point of Death, MI or Urgent Revascularization Hazard Ratios for Each Trial Comparing Abciximab Versus Placebo

	30 days				6 months			
	Placebo	Abciximab	OR (95% CI)	p Value	Placebo	Abciximab	OR	p Value
EPIC Men (%)	12.1	7.7	0.63 (0.42, 0.93)	0.02	16.6	11.4	0.66 (0.47, 0.93)	0.02
EPIC Women (%)	13.7	7.4	0.52 (0.28, 0.98)	0.05	19.2	12.0	0.59 (0.36, 1.00)	0.05
EPILOG Men (%)	11.3	5.0	0.43 (0.31, 0.60)	< 0.001	14.4	8.0	0.53 (0.40, 0.69)	< 0.001
EPILOG Women (%)	12.8	5.9	0.46 (0.28, 0.75)	0.002	15.5	9.4	0.58 (0.38, 0.88)	0.01
EPISTENT Men (%)	10.5	5.9	0.55 (0.39, 0.77)	0.001	11.6	7.3	0.61 (0.44, 0.83)	0.002
EPISTENT Women (%)	11.7	6.9	0.57 (0.33, 0.99)	0.05	13.6	9.5	0.67 (0.41, 1.10)	0.11

CI = confidence interval; OR = odds ratio.

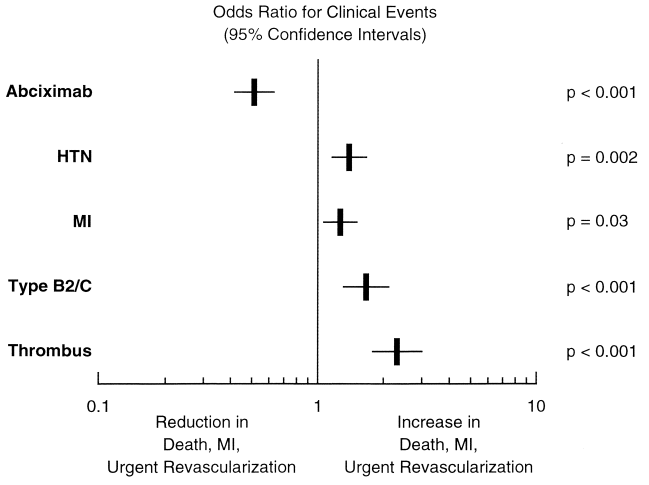

Figure 2. Clinical predictors of outcome after percutaneous coronary revascularization for the overall cohort. HTN = hypertension; MI = myocardial infarction.

ACC/AHA type B2 or C lesions and thrombus containing lesions.

Complications. Major bleeding events occurred in 2.9% versus 3.0% (p = 0.96) of women and 2.7% versus 1.3% (p = 0.003) of men treated with placebo versus abciximab, respectively. Minor bleeding events occurred in 4.7% versus 6.7% (p = 0.017) of women and 2.3% versus 2.2% (p = 0.94) of men treated with placebo versus abciximab, respectively (Table 3). However, there were no differences in rates of intracranial bleeding for women (0.0% vs. 0.3%, p = NS) or men (0.1% vs. 0.1%, p = NS) treated with placebo versus abciximab. The overall rates of bleeding and the gradient of bleeding risk with abciximab were markedly less in the treatment arms of EPILOG and EPISTENT, using reduced and weight-adjusted heparin dosing. Women had higher rates of major and minor bleeding complications with abciximab than men. Activated clotting time for women treated with abciximab were slightly higher than men treated with abciximab, 330 versus 326 (p = 0.3). However, the rate of major bleeding among women treated with abciximab was 3% compared with 1.3% in men (p = 0.004). Also, the rate of minor bleeding among women treated with abciximab was 6.7% versus 2.2% in men (p < 0.001, Fig. 3). While women had higher rates of bleeding with abciximab compared with men, they also had a higher rate of minor bleeding complications without abciximab than men, 4.7% versus 2.3% (p = 0.01) even though they had lower activated clotting time than men 368 versus 376 (p = 0.01) (Table 3).

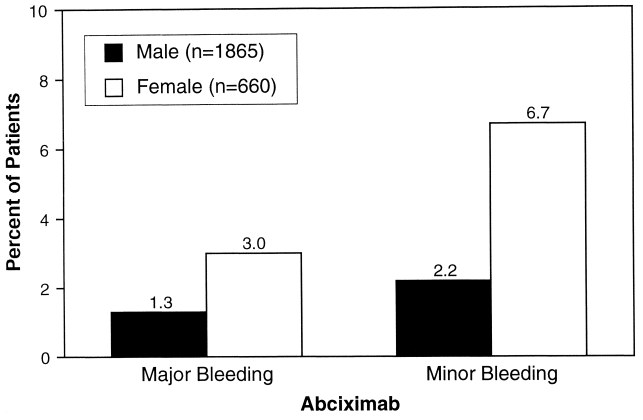

Figure 3. Major and minor bleeding event rates for patients treated with abciximab. p = 0.004 for major bleeding event; p < 0.001 for minor bleeding events.

A multivariate logistic regression model was developed using 20 clinical variables to determine the risk of bleeding (Fig. 4). Predictor of both major and minor bleeding was older age. However, there was a significant interaction between abciximab treatment, gender and bleeding outcome. Abciximab use, gender, body weight, race, smoking status and the use of aspirin, Ticlopidine or clopidogrel did not increase the risk of bleeding.

DISCUSSION

Summary. Our study examined collective data from three large randomized trials that enrolled, in aggregate, 6,595 patients undergoing percutaneous coronary revascularization. While women had more comorbidities, they derived equivalent treatment benefit with abciximab during PCI as did men at 30 days, six months and one year. We did not observe gender differences in clinical outcome after percutaneous intervention. The reduction in death, MI or urgent revascularization with abciximab was not gender specific at any time point.

However, women had a higher rate of major and minor bleeding with abciximab and heparin, even with low-dose, weight-adjusted heparin dosing compared with men. In the

Table 3. Bleeding Complications by Gender for Patients Receiving Abciximab

	Men			Women			
	Placebo (n = 1,277)	Abciximab (n = 1,865)	p Value*	Placebo (n = 471)	Abciximab (n = 660)	p Value†	p Value‡
Major (%)	2.7	1.3	0.003	2.9	3.0	0.96	0.004
Minor (%)	2.3	2.2	0.94	4.7	6.7	0.17	< 0.001
Non-CABG major (%)	0.8	0.7	0.64	1.8	1.4	0.61	0.08
Non-CABG minor (%)	2.2	2.2	0.97	4.3	6.6	0.11	< 0.001
Intracranial (%)	0.0	0.1	0.41	0.0	0.0	1.00	0.55

p value* = comparing male patients receiving placebo vs. abciximab; p value† = comparing female patients receiving placebo vs. abciximab; p value‡ = comparing male vs. female patients receiving abciximab.

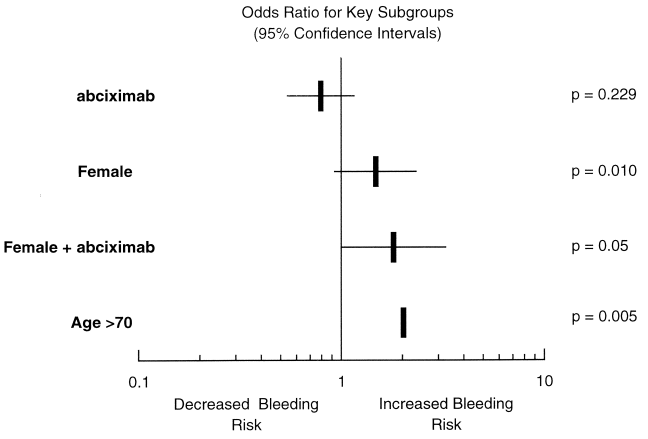

Figure 4. Clincal predictors of bleeding complications using low-dose heparin arm of EPILOG and the entire EPISTENT cohort.

multivariate logistic regression model, there was an interaction between abciximab treatment, gender and bleeding complications. Gender differences in bleeding complications after PCI have been described (18). A possible explanation may be due to gender specific response to anticoagulants. A prior work has shown increased partial thromboplastin time (PTT) for women with heparin, even after weight-adjusted dosing, suggesting an increased sensitivity to heparin among women (19).

Gender differences platelet aggregation. Platelet aggregation at the site of plaque rupture is a dominant feature in the pathophysiology of acute coronary syndromes and complications of percutaneous coronary revascularization. The final common pathway of platelet aggregation is the binding of fibrinogen to GP IIb/IIIa receptors on the surface of activated platelets leading to platelet thrombus (20). Several studies have suggested intergender differences in platelet response and reactivity, including a greater sensitivity of the platelets of women to aggregating stimuli (7,8,13). Recently, Faraday and associates (12) showed that platelets of women are capable of converting a greater proportion of available GP IIb/IIIa receptors to an activated state in response to both weak and strong agonists than are those of men. These investigators demonstrated a 50% to 80% increase in the number of activated receptor sites in women compared with men given the same agonist. Because women have more platelet reactivity, it is possible that they would derive greater benefit from a potent platelet inhibitor. In a small study, Goldschmidt-Clermont and associates (21) reported a greater reduction of ischemic events in female patients with acute coronary syndromes receiving eptifibatide, a GP IIb/IIIa inhibitor, than in men. While aspirin was adequate in reducing the ischemic state in men, women derived benefit only with GP IIb/IIIa inhibitor. This observation has not been confirmed, however, in large-scale trials of eptifibatide (22), tirofiban (23,24) or lamifiban (25). Moreover, the recent Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial showed that benefit with eptifibatide among patients with acute coronary syndromes was not observed in women treated outside North America (22). These conflicting findings have led to some confusion regarding the role of GP IIb/IIIa blockade in women.

Although there is an increased risk of minor bleeding with abciximab in women, these data demonstrate a significant treatment benefit with abciximab in reduction in death, MI and urgent revascularization, perhaps suggesting that all patients, regardless of gender, will derive important clinical benefit from abciximab.

Study limitations. Our study has a few key limitations. This was a retrospective analysis. Also, we did not perform a formal utility analysis. Lastly, in both the EPILOG and EPISTENT trials, there was a strict guideline for ACT and PTT range, for vascular access sites, as well as emphasis on early sheath removal; therefore, many of the variables that have been shown to affect bleeding complications were tightly controlled. Therefore, we lacked sufficient statistical power to perform detailed analysis on bleeding based on ACT or PTT range.

Conclusions. Over 240,000 women will receive either coronary stents or angioplasty this year. There has been some reluctance to use GP IIb/IIIa inhibition in women due to a perceived increased risk of complications and questionable benefit. Our study shows that women derive equivalent short- and long-term benefit from abciximab during percutaneous coronary intervention as do men. Although women had higher rates of both major and minor bleeding than did men with abciximab, major bleeding in women was similar with and without abciximab. A small increase in minor bleeding was observed with abciximab in women. The challenge lies ahead for optimizing the safety of percutaneous coronary intervention in women. Possible approaches for the future include combining GP IIb/IIIa blockade with other inhibitors of the thrombin cascade, which may present less of a hemorrhagic risk, such as bivalirudin or low molecular weight heparin.

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